REMARKS

Status of the Claims

Claims 48-50 and 55-70 are currently pending. Claims 57 and 58 are withdrawn from consideration. New claims 69 and 70 recite subject matter support in withdrawn claims 57 and 58, and depend from claim 55 as amended.

Regarding the Information Disclosure Statement

The applicants' file indicates that the Form 1449 to which the examiner refers in the office action was submitted January 23, 2004 and listed Refs. A1-A2, B1 and C1-C10. The examiner indicated that none of the "C" references were provided and were therefore not considered.

Each reference cited in the January 23, 2004 Form 1449 was made of record in parent US application Serial No. 09/700967 ("the '967 application") which issued as U.S. Patent 6,624,141, as evidenced by the fact that all of the "C" references are listed on the face of the issued patent.

If the examiner is unable to obtain copies of the previously submitted references from the parent application file, advice of the same is requested and applicants will gladly resubmit them.

Objection to the Specification

Applicants acknowledge the examiner's objection to the specification with regard to disclosed trademarks. Upon notice from the examiner of allowable subject matter, the applicants will provide an amended specification as requested.

Rejection of Claims under 35 USC §112, First Paragraph

The examiner rejected all pending claims under 35 USC 112, first paragraph, asserting that the claimed subject matter lacked written descriptive support in the specification.

The rejection was based on the examiner's assertions at pp. 5-6 of the office action,

> the claims are defined only by functional properties, not by a structure. Thus there is no indication of which purified protamine the claimed invention is directed to.
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> In addition the claims are directed to a method that utilizes the undefined protamine and a second coagulant which is also undefined. Furthermore the art teaches that protamine given to neutralize heparin after extracorporeal circulation can trigger a catastrophic reaction in some patients [citation omitted]. Therefore the claimed invention needs to adequately describe the protamine used in the invention.
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> Therefore a biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written descriptive purposes, even when accompanied by a method for obtaining the claimed sequence.
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> The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of encoded proteins, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method its isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel [complete citation omitted].

The applicants respectfully disagree. The examiner's assertion that the claims lack written description because the protamine utilized in the claimed method is defined only by functional properties overlooks the fact that protamines were well known in the art prior to the priority date of the present application and routinely used to neutralize heparin. The specification teaches, for example, at paragraph 14,

> [0014] To reduce post-operative bleeding, protamine, a clinical heparin antagonist, is routinely administered after cardiac and vascular surgery to reverse the anticoagulant activity of heparin (Jaques, 1973). Protamine consists of a group of heterogeneous polycationic peptides with an average molecular weight of about 4500 daltons. It is generally obtained from fish

> (Ando et al., 1973). Nearly 67% of the amino acid composition of protamine is arginine (Ando et al., 1973). The polycationic protamine combines electrostatically with the polyanionic heparin to form a stable complex that is devoid of anticoagulant activity.

Protamines were therefore know to be "a group of heterogeneous polycationic peptides" with "nearly 67%" of all amino acids being arginine, this arginine content providing the "polycationic" nature of the protein which "combines electrostatically with the polyanionic heparin to form a stable complex" neutralizing anticoagulant activity of heparin. Thus, while the exact primary structure, i.e., amino acid sequences, of protamines were acknowledged to variable, the specification teaches that the overall structure of protein has a high arginine content which imparts a polycationic characteristic to the protein and allows for its functional binding to heparin. In other words, the structure/function relationship for protamines was previously known.

What was not known, however, was that proteolytically cleaved protamine would have the same property of neutralizing heparin and provide the benefit of reduced toxic effects. The examiner alluded to "catastrophic reaction" in some patients receiving protamine treatment, but how this problem relates to written description is unclear. Regardless, the specification teaches that low molecular weight (LMW) protamines provide distinct advantages over higher molecular weight species, these LMW protamines being defined in paragraphs 32-35 in the specification. What is readily apparent from the disclosure is that LMW protamines useful to practice the invention need not have a specific amino acid sequence. They need only have a desired molecular weight and still be able to neutralize heparin, i.e., a sufficiently high cationic charge effective to neutralize heparin activity. In Example 2, the structure/function relationship for LMW protamine is discussed in detail in paragraph 178. Thus, given that it was known that full length protamines, i.e., those protamines which have not been reduced in size by whatever means, neutralize heparin because of a sufficiently polycationic charge, it naturally follows that the LMW protamines for use in the presently claimed methods possess the same polycationic characteristic in order to function in the same way.

With this knowledge about the relationship between structure and function of protamines, the applicants further submit that the specification would convey to the skilled

artisan that the applicants were in fact in possession of the invention as claimed. Having demonstrated possession of LMW protamines of a desired molecular weight in Example 1, the specification goes further to demonstrate that these LMW protamines neutralize heparin, also in Example 1 through use of the heparin sensor method [paragraphs 143-144] and chemical/biological assays [paragraphs 146-147] and in Example 2 [paragraph 160-161 and paragraphs 176-178].

Accordingly, the specification addresses each of the grounds relied on by the examiner for asserting a lack of written description. When these disclosures are combined with what the specification teaches was known in the art regarding the ability of protamines to neutralize heparin, the grounds for rejection are further rendered moot. Finally, when these disclosures and knowledge in the art are further combined with the experimental results expressly laid out in the examples, the worker of ordinary skill in the art would fully understand that the applicants were in fact in possession of the invention as claimed. Thus, the rejection of claims for alleged lack of written description must be withdrawn.

Rejection of Claims under 35 USC §112, Second Paragraph

The examiner rejected claims 48-50, 55-56 and 59-68 under 35 USC §112, second paragraph, for various reasons, each addressed separately below.

Claim 55 was rejected for reciting "a first purified protamine" with the examiner asserting that the term was unclear whether there is a second or subsequent protamine or the term indicates a first purification of the product. Amendment to claim 55 herein obviates the rejection.

Claim 55 was also rejected for reciting "reduced immunoresponsiveness or toxicity," the examiner stating that the term was unclear as to how much of a reduction was embraced. The applicants submit that the reduction is relative to that observed by "native protamine" as recited in the claims. How much of a reduction is irrelevant, as the claim embraces a relative reduction to any degree.

Claim 55 was also rejected for reciting the term "between about," the examiner asserting that "between" is a specific range and "'about' represents a range outside of the

between range." Similarly, the examiner asserted the phrase "molecular weight of between about 400 and about 2500" without a standard is unclear. The applicants have amended claim 55 to recite that the molecular weight is determinable using gel filtration. The amendment is supported in the specification by description of use of Sephadex G-25 [paragraph 140] which is a gel filtration resin. This amendment does not place a critical limitation on the method by which molecular weight *must* be determined; it merely provides a method that *can* be employed to determine if a specific LWM protamine falls within the scope of the claim. In other words, a would-be infringer does not avoid liability simply by using an alternative method for sizing LWM protamines used in an otherwise infringing method; if it is determined that a LWM identified using, for example SDS-PAGE, falls within the recited size range when using gel filtration, use of that LMW protamine would infringe nonetheless.

This amendment also obviates the examiner's other rejection based on recitation of "between about." The worker of ordinary skill in the art will readily appreciate that molecular weight sizing is inherently inexact. When sizing a compound using, for example, gel filtration against standards of known molecular weight, a determination of the precise size of the eluted compound depends on a number of factors including, for example, flow rate of the elution buffer and the amount of compound loaded onto a column; a slow elution rate or a large amount of compound loaded onto the column can give rise to a broad elution peak, and an elution profile that does result in a single, sharp peak gives rise only to an estimable molecular weight. Thus, the worker of ordinary skill would understand that the claim clearly recites approximate molecular weight endpoints and all weights in between. According, the amendment to recite a gel filtration determination obviates both rejections.

Claims 59-62 and 64 were rejected for assertedly lacking antecedent basis. The examiner's position was that claim 55 is directed to inactivating heparin and that the health condition of the mammal to which the inactivating agent is administered is not a step in the method. The applicants submit that the examiner is correct; the health of the mammal being treated is not a step in the method. However, the "health condition" of the recipient mammal is a limitation on the method as it further describes the type of mammal being treated. By analogy, if the independent claim simply recited "a patient" and a dependent claim defined the patient as "a mammal," the method of the independent claim would be

limited by the type of recipient patient, even though the steps of the method would otherwise be the same. The fact that the rejected dependent claims further describe the recipient mammal does not require that the steps of the method be altered in any way.

Accordingly, the applicants submit that that the rejection of claims under 35 USC §112, second paragraph, may properly be withdrawn.

Conclusion

In view of the amendments and remarks made herein, the applicants submit that the claims are in condition for allowance respectfully request notification of the same.

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Respectfully submitted,

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